## REMARKS

### Status of the Claims

Claims 18-33 are pending in this application.

Claim 29 is cancelled herein without prejudice or disclaimer of Applicants' right to represent the cancelled subject matter in this or a divisional application.

Claims 26 and 30 are amended herein. No new matter is introduced.

### Claim Objections

Claims 26 and 29 are objected to because of typographical errors. These typographical errors have been corrected in claim 26 in accordance with the Examiner's suggestions. Claim 29 has been cancelled. Therefore, Applicants respectfully request withdrawal of the objections.

### Claim Rejections

35 U.S.C. §112, second paragraph

Claims 26-32 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner states that the term 'corresponding' is not an art-recognized term to describe the relationship between two nucleic acid sequences or two polymorphism patterns. The Examiner indicates that this terms makes it unclear if reference is made to a polymorphism of the same identity and at the same nucleotide location on the genome, or if reference is made to a polymorphism of similar identity or similar location. In order to clarify these claims, they have been amended to remove the term "corresponding," and now recite "at the same chromosomal location as the position of the polymorphism amplified in (a)."

Claim 29 is rejected as indefinite. Applicants have cancelled claim 29, rendering this rejection moot.

Claims 30-32 are rejected as indefinite over the recitation of "typing blood relatives of a subject for a polymorphism" because the Examiner states that the claims do not recite how this step relates to the remainder of the claim. Applicants have amended the claims to include the

recitation, "analyzing the polymorphism by genetic linkage analysis for linkage to familial dysautonomia." Applicants therefore respectfully request that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

35 U.S.C. §112, First Paragraph: Written Description

Claims 20-33 are rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the claims do not define the structure of any polymorphisms located between D9S59 and D9S127 in terms of their nucleotide identity or location, and that they do not define the gene associated with familial dysautonomia in terms of a particular chemical structure. The Examiner explains that there are no teachings in the specification or the prior art as to the length of the gene, positions of the exons or introns, and so on. The Examiner also indicates that while Applicants were in possession of nine polymorphisms described in the specification, there is insufficient information provided in the specification to indicate that Applicants were in possession of the broadly claimed genus of any polymorphism in the region between D9S59 and D9S127 at the time of filing. Applicants respectfully traverse this rejection.

As an initial matter, Applicants point out that the instant invention is directed to genetic linkage analysis to identify individuals carrying the familial dysautonomia gene. Applicants have discovered the chromosomal location which carries the gene, which when defective, causes FD, and have identified the flanking markers for the gene as between D9S59 and D9S127. They have also identified numerous markers within this range that are closely and significantly linked to the FD gene (i.e., have a LOD score of greater than 3). An understanding of the exact nature of the gene responsible for a disease is not necessary in order to perform linkage analysis to identify polymorphisms which can serve as markers for the defective allele, and to identify individuals which are carriers for a hereditary disorder by detecting those specific polymorphisms. As stated in the instant specification, "[l]inkage analysis can be used to find the location of a gene causing a hereditary disorder and does not require any knowledge of the biochemical nature of the disease, i.e., the mutated protein that is believed to cause the disease..." (page 3, lines 25-29; emphasis added). The specification further states that "the location of the gene can be used for prenatal diagnosis even before the altered gene that causes the disease is found" (page 4, lines 10-12). Thus, what is necessary is the chromosomal location

of the defect responsible for the disease and polymorphisms within that location that, using well known genetic methods, have a high degree of association with the phenotype. This is exactly what the present application provides. Further, prior to identifying the FD gene, the knowledge of the marker polymorphisms associated with the gene has been used effectively in genetic counseling.

As described above, knowledge of the chemical structure of the gene associated with FD is not necessary in order to identify polymorphic markers associated with the defective gene and the disease associated therewith, or to use the markers identified in the instant invention for identifying individuals that carry the gene for FD. The Examiner also states that the structure of the markers located between the region flanked by D9S59 and D9S127 is not defined. Applicants respectfully direct the Examiner's attention to pages 22-23 of the specification which list the publications describing the structures of each of the markers used in the invention.

The Examiner contends that the seven polymorphisms disclosed in the application which are between the flanking markers of D9S59 and D9S127 are not sufficient to support the genus because the region spans 19 cM. Applicants respectfully disagree. Applicants have demonstrated with reasonable clarity to those skilled in the art that they were in possession of the claimed genus at the time of filing the application. Applicants have demonstrated possession of several different polymorphisms within a relatively small range on the q31 band of the long arm of human chromosome 9, all of which are significantly linked to the FD mutation and segregate with the FD phenotype, as shown by positive LOD scores. LOD scores express the probability that a marker is linked to a gene. Because the flanking markers, D9S59 and D9S127, are linked to the FD gene based on LOD score, by definition, polymorphisms within this range will have similar or better LOD scores than the flanking markers and will therefore be positively linked to the gene as well. The location of these polymorphisms, rather than their exact chemical structures is the important defining characteristic. In addition, the number of polymorphisms described is more than sufficient to demonstrate that Applicants were in possession of the claimed genus at the time of filing. The Examiner relies on Regents of University of Ca. v. Eli Lilly & Co. 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied 523 U.S. 1089 (1998) for the proposition that the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of

the claimed genus. What constitutes a "representative number of species" depends upon the knowledge and skill in the art. The knowledge and skill in the art would not require that an individual describe more polymorphisms than Applicants have described in the instant application. Moreover, such a description need not be sufficient to provide support to claim each individual species encompassed by the genus. Rather the description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568. It is clear that Applicants, with knowledge of the specific localized region on the chromosome combined with positive LOD scores, had possession of the necessary common attributes of the members of the genus.

The Examiner also indicates that Applicants' claims are directed to any polymorphisms within the recited range which are linked to a "wildtype or defective gene associated with familial dysautonomia." Applicants assert that the recitation "gene associated with familial dysautonomia" clearly makes reference to the defective, or mutated, gene associated with the FD phenotype, and that this parlance is well known to one of skill in the art. Only the defective gene is associated with the disease phenotype; the wildtype gene, by definition, is not associated with the disease phenotype. Therefore, the recitation "gene associated with familial dysautonomia" specifically and accurately refers only to the defective gene and would be interpreted as such by the skilled artisan. Applicants direct the Examiner's attention to the Notice of Allowability that the same Examiner issued in U.S. Patent No. 5,998,133 (U.S.S.N. 08/480,655) on June 15, 1999, in which the recitation of "gene associated with familial dysautonomia" in claims substantially similar to the instant claims was deemed acceptable for allowance and is interpreted as meaning the defective gene. The Examiner stated that the claims of the application were allowable over the prior art because:

> the prior art does not teach or suggest methods for detecting a polymorphism linked to a gene associated with familial dysautonomia (FD) wherein the methods comprise detecting a polymorphism on chromosome 9 between markers D9S53 and D9S105 wherein the presence of the polymorphism is indicative of an individual who is a carrier of a gene associated with FD (Notice of Allowability, June 15, 1999, page 2).

In view of at least the foregoing arguments, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

35 U.S.C. §112, First Paragraph: Enablement

Claims 20-33 are rejected under 35 U.S.C. §112, first paragraph. The Examiner states that while the specification is enabling for detecting the disclosed polymorphisms linked to a gene associated with FD, the claims are not enabled for detecting the presence of any polymorphism located between D9S59 and D9S127. Applicants respectfully traverse the rejection.

The Examiner provides an analysis using the Wands factors, and, throughout the analysis, makes reference to the fact that the specification does not actually define the specific location of the FD gene or define it in terms of structural features such as the nucleotide sequence of the gene. For example, the Examiner states that the

> specification does not provide any specific guidance as to how to identify a specific FD gene that is within the region of D9S59 to D9S127…[s]ince the polymorphisms are defined as being linked to the FD gene, and their presence is characterized as indicative of a carrier of a gene associated with FD, to practice the claimed invention requires a knowledge of a gene associated with the occurrence of FD. However, the specification does not provide sufficient guidance as to how to identify such a gene" (Office Action, page 13).

As described above in the "Written Description" section, the exact location of the gene and the structural features of the gene are not necessary for performing Applicants' invention. The invention is based on linkage analysis, the nature of which specifically does not require the knowledge of the specific attributes or even the precise location of the gene in question, because the polymorphisms identified segregate with the FD phenotype and have significant LOD scores such that they can be used in genetic screening tests for FD. Performing genetic screening using the markers identified as associated with the FD gene as described in the application does not require more than has been disclosed in the instant application. The instant claims are not directed to identifying an FD gene, and, as stated above, this is not necessary information for carrying out the claimed invention.

The Examiner also contends that the number of working examples is not sufficient for detection of any polymorphisms within the claimed region of D9S59-D9S127 that are associated with any wildtype or mutated genes associated with FD. As explained above in the "Written Description" section, Applicants assert that the recitation "gene associated with familial dysautonomia" clearly makes reference to the defective, or mutated, gene associated with the FD phenotype, and that this parlance is well known to one of skill in the art so that it is clearly understood by the skilled artisan that only the defective gene is associated with the disease phenotype. Therefore, one of skill in the art would understand that the claims are directed to the detection of polymorphisms associated with the mutated FD gene. With respect to the working examples, Applicants have provided nine examples of polymorphisms that segregate with the FD phenotype as indicated by LOD score. This is more than sufficient to enable one of skill in the art to determine additional polymorphisms that are associated with the FD gene mutation. Genetic linkage analysis techniques are well known to those of skill in the art and are described extensively throughout the instant specification. As described above, because the flanking markers, D9S59 and D9S127, are linked to the FD gene based on LOD score, by definition, polymorphisms within this range will be positively linked to the gene based on LOD score as well. Applicants have significantly narrowed the range in which to search for polymorphisms associated with FD in the instant application, and have provided more than sufficient disclosure to enable one of skill in the art to determine additional makers associated with the FD gene within the claimed genus.

Applicants respectfully request that based on at least the foregoing, the rejections under 35 U.S.C. §112 be withdrawn.

## Nonstatutory Type Double Patenting

Claims 20-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,998,133 and claims 1-16 of U.S. Patent No. 5,387,506. Without agreeing with the Examiner's characterization of the claims, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter.

35 U.S.C. §102(a)

Claims 20-25 and 30-33 are rejected under 35 U.S.C. §102(a) as being anticipated by Kwiatakowski. Applicants respectfully traverse the rejection.

The Examiner states that Kwiatakowski describes a method for detecting the presence of a D9S59 polymorphism, and that an inherent property of this polymorphism is that it is linked to a gene associated with FD. Kwiatakowski describes the nucleic acid sequence for detecting D9S59, but does not teach or suggest that this polymorphism is linked to the FD gene, or that this marker can be used to identify individuals carrying the gene associated with FD. The instant claims are directed to methods for detecting the presence of polymorphisms linked to the gene associated with FD, and are therefore not anticipated by Kwiatakowski.

In addition, Applicants point out that the Examiner of this application also allowed Patent Nos. 5,998,133 and 5,387,506, both of which were initially rejected as anticipated by Kwiatakowski, and were subsequently allowed over this art. Both of these patents have substantially similar claim language to the instant claims with respect to the method claims, as described above, except for the recited markers. In the Notice of Allowability for the 5,998,133 patent, mailed June 21, 1999, the same Examiner that is examining the instant application stated that:

> [t]here are no teachings in the prior art which localize the gene linked to familial dysautonomia to 9q. Accordingly, [the claims] are allowable over the prior art because the prior art does not teach or suggest methods for detecting a polymorphism linked to a gene associated with familial dysautonomia (FD) wherein the methods comprise detecting a polymorphism on chromosome 9 between markers D9S53 and D9S105 wherein the presence of the polymorphism is indicative of an individual who is a carrier of a gene associated with FD (Notice of Allowability, June 15, 1999, page 2).

In view of at least the foregoing, Applicants respectfully request withdrawal of this ground of rejection.

## CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

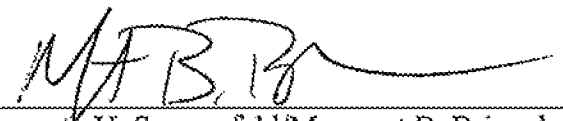
## AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3732, Order No. 13572.105040.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 13572.105040.

Respectfully submitted,
KING & SPALDING LLP

Dated: October 10, 2007

By: 

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